Claims

1. A tissue-adhesive formulation consisting of a naturally occurring or synthetic polymerisable and/or cross-linkable material in particulate form, the polymerisable and/or cross-linkable material being in admixture with particulate material comprising tissue-reactive functional groups.

2. A formulation according to Claim 1, wherein the ratio of polymerisable and/or cross-linkable material to material comprising tissue-reactive functional groups is between 0.1:1 and 10:1.

3. A formulation according to Claim 2, wherein the ratio of polymerisable and/or cross-linkable material to material comprising tissue-reactive functional groups is between 0.2:1 and 1:1.

4. A formulation according to any preceding claim, wherein the tissue-reactive functional groups are selected from the group consisting of imido ester, p-nitrophenyl carbonate, N-hydroxysuccinimide ester, epoxide, isocyanate, acrylate, vinyl sulfone, orthopyridyl-disulfide, maleimide, aldehyde and iodoacetamide.

5. A formulation according to Claim 4, wherein the tissue-reactive functional groups are N-hydroxysuccinimide esters.

6. A formulation according to any preceding claim, wherein the formulation contains one type of material comprising tissue-reactive functional groups.

7. A formulation according to any one of Claims 1 to 5, wherein the formulation contains two types of materials comprising tissue-reactive functional groups.

8. A formulation according to any preceding claim, wherein the material comprising tissue-reactive functional groups is formed by derivatization of a polymer precursor.

9. A formulation according to Claim 8, wherein all or substantially all of the available sites in the polymer precursor are derivatised.

10. A formulation according to Claim 8 or Claim 9, wherein the polymer precursor contains carboxylic acid or alcohol functional groups.

11. A formulation according to Claim 10, wherein the polymer precursor is selected from the group consisting of sucrose, cellulose and polyvinylalcohol.

12. A formulation according to Claim 10, wherein the polymer precursor is formed by polymerisation of two or more monomers, and at least one of the monomers contains a carboxylic acid group or a group capable of being reacted with another material to form an acid functionality.

13. A formulation according to Claim 12, wherein the monomers are selected from the group consisting of *N*-vinyl-2-pyrrolidone, acrylic acid, vinyl acetate, vinyl acetic acid, mono-2-(methacryloyloxy)ethyl succinate, methacrylic acid, 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate and (polyethylene glycol) methacrylate.

14. A formulation according to Claim 12 or Claim 13, wherein polymerisation is initiated by a free radical initiator.

15. A formulation according to Claim 14, wherein the initiator is selected from the group consisting of benzoyl peroxide, 2,2'-azobisisobutyronitrile, lauroyl peroxide and peracetic acid.

16. A formulation according to any one of Claims 12 to 15, wherein the polymer precursor is poly(N-vinyl-2-pyrrolidone-co-acrylic acid) co-polymer.

17. A formulation according to Claim 16, wherein the poly(N-vinyl-2-pyrrolidone-co-acrylic acid) co-polymer has a molar ratio of acrylic acid-derived units less than 0.60, more preferably less than 0.40.

18. A formulation according to Claim 16, wherein the poly(N-vinyl-2-pyrrolidone-co-acrylic acid) co-polymer has a molar ratio of acrylic acid-derived units between 0.025 and 0.25.

19. A formulation according to any one of Claims 7 to 18, wherein the polymer precursor is derivatised with N-hydroxysuccinimide to form the material comprising tissue-reactive functional groups.

20. A formulation according to Claim 19, wherein the material comprising tissue-reactive functional groups is an N-hydroxysuccinimide ester of poly(N-vinyl-2-pyrrolidone-co-acrylic acid) co-polymer.

21. A formulation according to Claim 20, wherein the material comprising tissue-reactive functional groups has a molar ratio of acrylic acid-derived units between 0.05 and 0.50 and vinyl pyrrolidone-derived units between 0.50 and 0.95.

22. A formulation according to any preceding claim, wherein the concentration of material comprising tissue-reactive functional groups in the formulation is between 10 and 50% w/w.

23. A formulation according to any preceding claim, wherein the polymerisable and/or cross-linkable material is selected from the group consisting of polysaccharides, polylactates, polyols and proteins, and derivatives thereof.

24. A formulation according to any one of Claims 1 to 22, wherein the polymerisable and/or cross-linkable material is, or further comprises, a chemically modified polyalkylene glycol containing multiple primary amino or thiol groups.

25. A formulation according to Claim 23, wherein the polymerisable and/or cross-linkable material is cross-linked.

26. A formulation according to Claim 23 or Claim 25, wherein the polymerisable and/or cross-linkable material is albumin.

27. A formulation according to Claim 26, wherein the polymerisable and/or cross-linkable material is porcine, bovine or human albumin.

28. A formulation according to any preceding claim, wherein the polymerisable and/or cross-linkable material is buffered to a pH greater than 7.

29. A formulation according to any preceding claim, further comprising one or more further components selected from structural polymers, surfactants, plasticisers and other excipients.

30. A formulation according to any preceding claim, wherein the particles that make up the formulation have a median size in the range 5μm to 500μm, more preferably 5μm to 100μm.

31. A sheet having a multilayer structure, said structure consisting of a core of a naturally occurring or synthetic polymeric material, the core being coated on at least one side thereof with a tissue-adhesive formulation according to any preceding claim.

32. A sheet according to Claim 31, wherein the core comprises a polymeric material selected from the group consisting of polymers or co-polymers based on

α-hydroxy acids such as polylactide, polyglycolide, polycaprolactone and other polylactones such as butyro- and valerolactone.

33. A sheet according to Claim 31, wherein the core comprises polymeric material selected from the group consisting of alginates, polyhydroxyalkanoates, polyamides, polyethylene, propylene glycol, water-soluble glass fibre, starch, cellulose, collagen, pericardium, albumin, polyester, polyurethane, polyetheretherketone, polypropylene and polytetrafluoroethylene.

34. A sheet according to any one of Claims 30 to 33, wherein the core is apertured.

35. A sheet according to Claim 34, wherein the sheet has a regular array of apertures, and the apertures are between 50μm and 2mm in diameter and adjacent apertures are formed at a centre-to-centre separation of between 100μm and 5mm.

36. A sheet according to Claim 35, wherein the apertures account for between 5% and 80% of the overall surface area of the core.

37. A sheet according to any one of Claims 30 to 36, wherein the core has a thickness of 0.005 to 5mm.

38. A sheet according to any one of Claims 30 to 37, wherein the tissue-adhesive formulation is applied to the core by mechanically compressing a blend of material containing tissue-reactive functional groups and polymerisable and/or cross-linkable material, both in particulate form, onto one or both sides of the core.

39. A sheet according to Claim 38, wherein the core is coated on both sides with the said blend of material.

40. A sheet according to Claim 39, wherein one surface of the sheet is coated with a non-adhesive material.

41. A sheet according to Claim 40, wherein the non-adhesive material is selected from the group consisting of polyethylene glycols, polylactide and poly(lactide-co-glycolide).

42. A sheet according to Claim 41, wherein the non-adhesive coating includes a visibly-absorbing chromophore.

43. A sheet according to Claim 42, wherein the visibly-absorbing chromophore is methylthioninium chloride.

44. A sheet according to any one of Claims 40 to 43, wherein the coating of non-adhesive material is apertured.

45. A biocompatible and hydratable composition suitable for topical application to internal or external surfaces of the body, which composition comprises a polymer containing tissue-reactive functional groups and a polymer containing groups that are not tissue-reactive functional groups but which are capable of forming hydrogen bonds with groups at the surface of a tissue to which the matrix is applied.

46. A composition as claimed in Claim 45, wherein the tissue-reactive functional groups are selected from the group consisting of imido ester, p-nitrophenyl carbonate, N-hydroxysuccinimide ester, epoxide, isocyanate, acrylate, vinyl sulfone, orthopyridyl-disulfide, maleimide, aldehyde and iodoacetamide, and the groups that are capable of forming hydrogen bonds are selected from amide, lactam, carbonyl, carboxyl, hydroxyl and ether groups.

47. A composition as claimed in Claim 45 or Claim 46, wherein the tissue-reactive groups and the groups that are capable of forming hydrogen bonds are present in the same polymer.

48. A composition as claimed in Claim 47, wherein the tissue-reactive groups are tissue-reactive ester groups, and the groups that are capable of forming hydrogen bonds are amide or lactam groups.

49. A composition as claimed in Claim 48, wherein the polymer is activated PVP-co-PAA.

50. A composition as claimed in Claim 49, wherein the polymer is NHS-activated PVP-co-PAA.

51. A composition as claimed in any one of Claims 45 to 50, which has the form of a sheet, patch, film or the like.

52. A method for the manufacture of a sheet according any one of Claims 31 to 44, which method comprises forming a core consisting of naturally occurring or synthetic polymeric material, and coating at least one side of said core with a tissue-adhesive formulation comprising a blend of a naturally occurring or synthetic polymerisable and/or cross-linkable material in particulate form and particulate material consisting of tissue-reactive functional groups.

53. A method of joining a tissue surface to another tissue, or of sealing a tissue surface, which method comprises applying to the tissue surface a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51.

54. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 to enhance wound healing.

55. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 to promote wound closure.

56. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 to provide reinforcement in hernia repair procedures.

57. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 for sealing of joined tubular structures such as blood vessels.

58. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 in sealing resected tissue surfaces.

59. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 for sealing air leaks in the lung.

60. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 to promote haemostasis.

61. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 for delivering a drug or other therapeutic agent.

62. Use of a formulation according to any one of Claims 1 to 30, a sheet according to any one of Claims 31 to 44 or a composition according to any one of Claims 45 to 51 for preventing post-surgical adhesions.